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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/772,103	01/26/2001	Beatriz M. Carreno	GNN-009CP	7957

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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/772,103	CARRENO ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 – 11 and 13 – 24* is/are pending in the application.

4a) Of the above claim(s) *16 – 23* is/are withdrawn from consideration.

5)☒ Claim(s) *14 and 15* is/are allowed.

6)☒ Claim(s) *2-11, 13, 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Ilia Ouspenski, Group Art Unit 1644, Technology Center 1600.

2. Applicant's amendment, filed 05/28/2004, is acknowledged and has been entered.

Claims 1 and 12 have been cancelled.

Claims 2, 4, and 7 have been amended.

Claims 16 – 23 have been withdrawn from consideration as being drawn to non-elected invention.

Claims 2 – 11 and 13 – 24 are pending.

Claims 2 – 11, 13 – 15, and 24 are under consideration in the instant application.

3. This Office Action will be in response to applicant's arguments, filed 05/28/2004.

The rejections of record can be found in the previous Office Actions.

The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.

It is noted that New Grounds of Rejection are set forth herein.

4. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R. § 1.75(d)(1) and M.P.E.P. § 608.01(l). Correction of the following is required:

Applicant is requested to identify the written support for amended claim 7, particularly the claimed limitation of "reduced binding of the antibody to the human CTLA4 with the substitution of amino acid 83."

Alternatively, Applicant is invited to amend the specification to provide proper antecedent basis for the claimed subject matter.

5. The disclosure stands objected to because of the following informalities: "Blanks" are present in the specification on pages 4, 5 and 28 for ATCC and hybridoma designations of the CTLA4 antibodies.

Applicant's request to hold correction in abeyance until such time as the ATCC designations can be provided is acknowledged.

Appropriate correction is required but held in abeyance.

6. Applicant's amendment to remove New Matter from claim 7 has obviated the previous rejection of claim 7 under 35 U.S.C. 112 first paragraph.

7. Claims 2 – 7, 10, 11, 13, and 24 are rejected under 35 USC 102(e) as being anticipated by Korman et al. (US 2002/0086014, of record, see entire document).

Applicant's arguments filed 05/28/2004 have been fully considered but were not found convincing.

Applicant asserts the Korman reference does not anticipate the claimed invention because its priority document (provisional application 60/150,452) does not disclose each and every element as set for the in the amended claim either expressly or inherently.

Contrary to Applicant's assertions, the provisional application 60/150,452 teaches anti-CTLA-4 antibodies, including monoclonal and humanized antibodies, including conjugated therapeutic moieties, such as chemotherapeutics and toxins (e.g. abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin) (page 9 paragraph 3, page 31 paragraph 3, and especially page 38 paragraph 2). In addition, the provisional application teaches an antibody that blocks binding of CTLA-4 to B7 (see e.g. claim 7, page 62), and soluble IgG antibodies to CTLA-4 (page 48, paragraphs 2 and 3). Although the reference teaches that naked soluble antibodies to CTLA-4 can promote the expansion of T cells (page 48 paragraph 2), an inherent property of the same antibodies when conjugated to a toxin will be to kill target cells, thereby inhibiting their proliferation. Thus given the description of anti-CTLA-4 antibodies disclosed by Korman et al. in the provisional application 60/150,452, the claimed specificity and functional properties recited in claims 2 – 6, 10, 11, 13, and 24 are inherent properties of prior art anti-CTLA-4 antibodies. Also inherent is the property of reduced binding to a mutant antigen, recited in claim 7, especially in the absence of evidence to the contrary.

The rejection is maintained essentially for the reasons of record, as applied to the amended claims.

8. Claims 2, 10, 11, 13 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Lowman et al. (U.S. Patent No. 5,994,511; of record, see entire document).

Applicant's arguments filed 05/28/2004 have been fully considered but were not found convincing.

Lowman et al. teach antibodies against a variety of antigens, including CTLA-4 (see column 29, paragraph 1), including monoclonal and humanized antibodies (see columns 31-57) as well as Immunoconjugates (e.g., diphtheria A chain, ricin, abrin, see column 43) (see entire document, including Detailed Description of the Invention).

Applicant argues that since some CTLA4 antibodies stimulate an immune response, the allegation that any CTLA4 specific antibody would possess the functional limitations of inhibiting T cell proliferation must fail.

As discussed infra in regard to the Korman reference, an inherent property of any toxin-conjugated antibody which binds to cells of a specific type will be to kill target cells, thereby inhibiting their proliferation, regardless of the possible effect of the corresponding naked antibody.

9. Claims 2 – 11, 13, and 24 are rejected under 35 USC 103(a) as being unpatentable over Korman et al. (US 2002/0086014, of record, see entire document) and further in view of Hamann et al. (US pat. No. 5,773,001, of record, see entire document).

Applicant argues that Korman et al. teach away from using soluble anti-CTLA-4 antibodies to inhibit T cell proliferation. This argument has been addressed infra to conclude that while it applies to naked anti-CTLA-4 antibodies, the opposite will be the case when the same antibodies are conjugated to a toxin.

Korman et al. have been discussed infra and teach anti-CTLA-4 antibodies, including monoclonal and humanized antibodies, including conjugated therapeutic moieties, such as chemotherapeutics and various toxins, and antibodies that block binding of CTLA-4 to B7 and soluble IgG antibodies to CTLA-4.

Korman et al. do not teach anti-CTLA-4 antibody-toxic moiety conjugate wherein the toxic moiety is a carbohydrate or, more specifically, caliheamicin.

Hamann et al. teach that calicheamicin is a potent toxin that can be conjugated to antibodies and used to eliminate cells expressing the antigen recognized by the antibody of the conjugate (e.g. columns 6 – 20).

One of ordinary skill in the art at the time the invention was made would have been motivated to select from the various known toxic moieties, including carbohydrates such as calichamicin, bacterial products such as ricin A chain and saporin and chemotherapeutics in combining anti-CTLA-4 antibodies and toxic moieties to target CTLA-4 expressing T cells and inhibit their proliferation. From the teaching of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. Claims 2-11, 13 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godfrey et al. (U.S. Pat. No. 5,821,332, of record) and Kuchroo et al. (U.S. Pat. No. 6,207,156, of record), and further in view of Hamann et al. (U.S. Pat. No. 5,773,001, of record) for the reasons of record.

Applicant's arguments, filed 05/28/2004, have been fully considered but have not been found convincing. Applicant argues that there is no reasonable expectation of success nor motivation in combining the cited references.

Applicant's arguments and the examiner's rebuttal are essentially the same of record. The rebuttal of record is reiterated supra.

Applicant argues that the teachings of Hamann et al. do not compensate for the deficiencies of Godfrey et al. and Kuchroo et al.

Applicant argues that there is not motivation to combine the teachings of Godfrey et al. with that of Kuchroo et al. because Godfrey et al. teach antibody-toxin conjugates for the purpose of eliminating cells and suppressing an undesired immune response, while Kuchroo et al. teach that anti-CTLA4 antibodies are useful as immune response enhancers.

The claims are drawn to an antibody-toxic moiety conjugate comprising a humanized monoclonal antibody that specifically recognizes human CTLA4, including wherein the antibody blocks binding of CTLA4 to CD80 or CD86.

As previously noted, Godfrey et al. teach the human polypeptide ACT-4 and that this receptor is expressed only on the surface of activated CD4 T cells, its expression being absent on resting T cells as well as on other cell types in physiological conditions (see entire document, but especially columns 9-10 and in particular column 10 at lines 11-17).

Godfrey et al. also teach antibodies to the human ACT-4 protein, including monoclonal antibodies and humanized monoclonal antibodies (see especially columns 14-18).

Godfrey et al. teach that the anti-ACT-4 antibodies can be conjugated to a toxic moiety for use as an immunotoxin (see especially the bridging paragraph of column 17-18). Godfrey et al. teach that there are many suitable toxin components (column 18 at lines 6-11), including the bacterial toxin ricin (column 18 at lines 6-11 in view of column 10 at lines 47-49).

Godfrey et al. teach that immunotoxins comprising anti-ACT-4 antibodies, including humanized anti-Act-4 antibodies, can be used as therapeutic reagents to suppress undesired immune responses by selectively eliminating activated CD4 T cells (see entire document, but especially column 22 at lines 11-36). Godfrey et al. teach that therapeutic agents which selectively eliminate activated cells are particularly advantageous because such reagents eliminate the cells involved in the undesired immune response while sparing non-activated T cells and preserving a residual immune capacity (see comments at column 22 lines 27-36).

Godfrey et al. review in column 2 the art-recognized motivation for developing multiple reagents which targeted different cell-surface receptors for use in methods of suppressing undesired immune responses. In particular, Godfrey et al. note that when using a single therapeutic agent to suppress an undesired immune response in a patient the patient may develop an immune response to the agent which prevents its effect and that cells expressing the target antigen may adapt to the therapy by ceasing to express the target antigen.

Finally, Godfrey et al. also note that the art recognized that while it was desirable to develop multiple reagents, the ideal reagents block only undesired immune responses while leaving a residual capacity to effect desirable immune responses (see especially comments at column 2, lines 7-40).

Kuchroo et al. teach monoclonal antibodies to human CTLA4 which bind to CTLA4 and prevent the interaction of B7 with human CTLA4 (see entire document, e.g., "Summary of the Invention" at columns 2-4). Kuchroo et al. teach that the anti-human CTLA4 monoclonal antibodies may be humanized (e.g., column 2 at lines 48-60 and columns 7-9). Kuchroo et al. review that CTLA4 is a molecule expressed only on activated T cells (see comment at column 1, lines 60-67). Kuchroo et al. further review that "B7" includes B7-1 and B7-2 (e.g., column 1 at lines 27-50). B7-1 is an alternate name for CD80 and B7-2 is an alternate name for CD86.

Kuchroo et al. do not teach an antibody-toxic moiety conjugate comprising a humanized monoclonal antibody that specifically recognizes human CTLA4, including wherein the antibody blocks binding of CTLA4 to CD80 or CD86.

The Examiner has previously argued that given the teachings of Godfrey et al. that it was desirable to produce toxins conjugated to different antibodies which each targeted different cell surface molecules expressed selectively on cells involved in undesired immune responses in order to eliminate the cells in vivo and the teachings of Kuchroo et al. of antibodies to the CTLA4 antigen expressed on activated T cells; it would have been obvious to the ordinary artisan at the time the invention was made to produce antibody-toxin moiety conjugates comprising the anti-CTLA4 antibodies of Kuchroo et al.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (S.D. N.Y. 1979); and In re Burckel 201 USPQ 67 (CCPA 1979).

That Kuchroo et al. teach the enhancement of an immune response using anti-CTLA4 antibodies not conjugated to a toxic moiety does not alter the fact that Kuchroo et al. also teach that CTLA4 is molecule expressed only on activated T cells. Viewed in the context of the teachings of Godfrey et al., the ordinary artisan would have appreciated that even though in certain instances antibodies to CTLA4 may be used to enhance an immune response, CTLA4 could also serve as a target for the elimination of T cells when the T cells were participating in an undesired immune response.

As noted supra, Godfrey et al. teach that many different toxins are suitable for conjugating to antibodies, and points in particular to the bacterial product ricin (column 18 at lines 6-11). As also noted supra, the antibodies of Kuchroo et al. prevent the interaction of B7 with human CTLA4 (see entire document, e.g., "Summary of the Invention" at columns 2-4). In addition, the antibodies of Kuchroo, because they do prevent the interaction of B7 with human CTLA4 would also necessarily bind to a region of the CTLA4 molecule in spatial proximity to the site of CTLA4 binding to a costimulatory molecule. Similarly, binding of the antibodies of Kuchroo et al. would necessarily be modulated by a substitution in CTLA4 at position 83 of SEQ ID NO:2.

Applicant has argued that there was no reasonable expectation of success in combining the teachings of Godfrey et al. and Kuchroo et al. because ACT4 is a member of a different family of molecules than CTLA4 and ACT4 is "unique" among activation antigens.

The Examiner has previously noted that the ordinary artisan would have had a reasonable expectation of producing the instant antibody-toxic moiety conjugate given the availability of the anti-CTLA4 antibodies of Kuchroo et al. and the standardized techniques for conjugating any of a variety of toxic moieties to an antibody.

It is further noted that the instant claims are drawn to a product. The motivation of the ordinary artisan to produce the instantly claimed product would also not have been inhibited by the fact that CTLA4 and ACT4 belong to different receptor families or the "uniqueness" of ACT4. Antibody linked toxins to a variety of receptor families were well known in the art at the time the invention was made for depletion of various cell types. The identification of cell surface molecules expressed predominantly on activated T cells provided the ordinary artisan with an opportunity to selectively eliminate activated T cells, but spare T cells not involved in the undesired immune response. As noted supra, Godfrey et al. clearly teach the desirability of selective targeting, and the desirability of targeting more than one receptor.

As previously noted, Godfrey et al. teach that any of a number of toxins are suitable components of an antibody-toxic moiety conjugate (column 18 at lines 6-11).

Hamann et al. teach that calicheamicin is a potent toxin that can be conjugated to antibodies, including humanized antibodies, and used to eliminate cells expressing the antigen recognized by the antibody of the conjugate (see entire document, especially "Background of the Invention" at columns 6-20).

The Examiner maintains that it would therefore have been obvious to the ordinary artisan at the time the invention was made to substitute the carbohydrate calicheamicin for the toxin moiety of the antibody-toxin immunoconjugate taught by Godfrey et al. and Kuchroo et al. The ordinary artisan would have been motivated to make such a substitution in view of the recognized suitability of calicheamicin in antibody-toxin conjugates, and because Hamann et al. teach that calicheamicin is a potent toxin. Given the teaching of antibody- calicheamicin conjugates by Hamann et al., the ordinary artisan would have had a reasonable expectation that the antibodies of Kuchroo et al. could also be conjugated to calicheamicin to produce antibody-toxic moiety conjugate comprising an antibody that specifically recognizes CTLA4 and a toxic moiety that is the carbohydrate calicheamicin. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The amendments to the instant claims do not appear to alter the rejection of record. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been fully persuasive.

11. Claims 14 and 15 appear to be allowable.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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July 23, 2004